BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [5]: C07D 263/58, 213/74, 239/42, A61K 31/42, 31/44, 31/505

A1

(11) International Publication Number: WO 94/29285

(43) International Publication Date: 22 December 1994 (22.12.94)

(21) International Application Number: PCT/EP94/01449

(22) International Filing Date: 3 May 1994 (03.05.94)

(30) Priority Data:
9311661.4 5 June 1993 (05.06.93) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: FALLER, Andrew [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

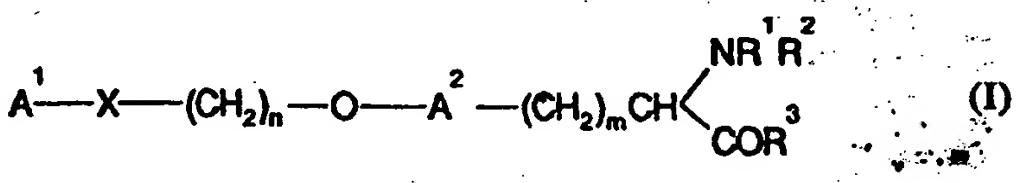
(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: HETEROCYCLIC DERIVATIVES AND THEIR USE IN PHARMACEUTICALS

(57) Abstract

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein: A^1 represents a substituted or unsubstituted aromatic heterocyclyl group; A^2 represents a benzene ring having three optional substituents; R^1 represents a hydrogen atom or an alkyl group; R^2 represents an aryl group; R^3 represents OT^1 wherein T^1 represents hydrogen, alkyl, aryl or aralkyl, or R^3 represents NR^4R^5 wherein R^4 and R^5 each independently represent hydrogen or alkyl or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring; X represents O, S or NR wherein R represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; m represents an integer in the range of from 1 to 6; and n represents an integer in the range of from 2 to 6; a process for preparing such a compound, a composition comprising such a compound and the use of such a compound and composition in medicine.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

HETEROCYCLIC DERIVATIVES AND THEIR USE IN PHARMACEUTICALS

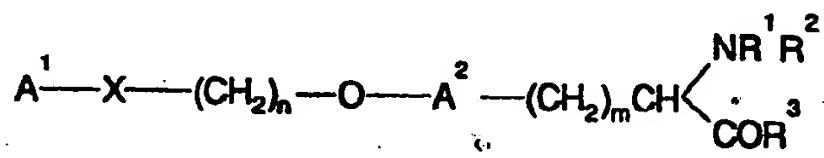
This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

International Patent Applications, Publication Number WO 91/19702 and WO 94/01420 discloses certain heterocyclic compounds which are stated to be of potential use in the treatment and/or prophylaxis of hyperglycaemia, especially Type II diabetes

It has now surprisingly been discovered that certain novel compounds show good blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension and cardiovascular disease, especially atherosclerosis. In addition these compounds are indicated to be useful for the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

A^2 represents a benzene ring having three optional substituents;

R^1 represents a hydrogen atom or an alkyl group;

R^2 represents an aryl group;

R^3 represents OT^1 wherein T^1 represents hydrogen, alkyl, aryl or aralkyl, or R^3 represents-NR^4R^5 wherein R^4 and R^5 each independently represent hydrogen or alkyl or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring;

X represents O, S or NR wherein R represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
m represents an integer in the range of from 1 to 6; and
n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

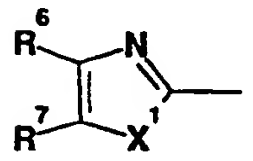
In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

Suitable values for A^1 when it represents a 5- membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

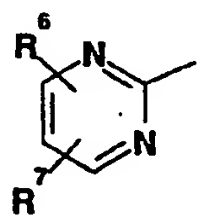
Suitable values for A^1 when it represents a 6- membered aromatic heterocyclyl group include pyridyl or pyrimidinyl, especially pyridyl.

A particular pyridyl group is a 2-pyridyl group.

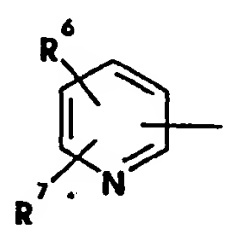
Preferably, A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

wherein:

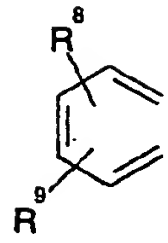
R^6 and R^7 each independently represents a hydrogen or halogen atom, an alkyl or alkoxy group or a substituted or unsubstituted aryl group or when R^6 and R^7 are each attached to adjacent carbon atoms, then R^6 and R^7 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^6 and R^7 together may be substituted or unsubstituted; and in the moiety of formula (a)
X^1 represents oxygen or sulphur.

Aptly, A^1 represents a moiety of the abovedefined formula (a).

Aptly, A^1 represents a moiety of the abovedefined formula (b).

Aptly, A^1 represents a moiety of the abovedefined formula (c).

In one favoured aspect R^6 and R^7 together represent a moiety of formula (d):



(d)

wherein R^8 and R^9 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^8 and R^9 each independently represent hydrogen, halogen, alkyl or alkoxy. Favourably, R^8 represents hydrogen. Favourably, R^9 represents hydrogen. Preferably, R^8 and R^9 both represent hydrogen.

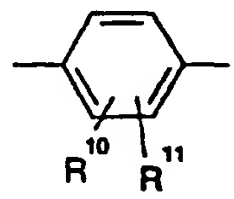
In a further favoured aspect R^6 and R^7 each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group and more favourably, R^6 and R^7 each independently represent hydrogen, alkyl or phenyl.

Preferably, for the moiety of formula (a), R^6 and R^7 together represent the moiety of formula (d).

Preferably, for the moieties of formula (b) or (c), R^6 and R^7 both represent hydrogen.

Favoured optional substituents for A^2 are selected from the group consisting of halogen, substituted or unsubstituted alkyl and alkoxy.

Favourably, A^2 represents a moiety of formula (e):



(e)

wherein R^{10} and R^{11} each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^{10} and R^{11} each independently represent hydrogen, halogen, alkyl or alkoxy. Preferably, R^{10} and R^{11} each represent hydrogen.

In one aspect, X represents O. In a further aspect, X represents S. In yet a further aspect, and preferably, X represents NR.

Suitably ,R^1 is hydrogen or C_{1-6} alkyl.

Examples of R^1 include hydrogen and ethyl.

Suitably, R^2 represents aryl, especially phenyl.

In one aspect, R^3 represents OT^1.

T^1 is suitably C_{1-6} alkyl.

An example of T^1 is methyl.

In one aspect, R^3 represents $-NR^4R^5$ wherein R^4 and R^5 are as defined above.

Suitably, R^4 and R^5 each independently represent hydrogen or C_{1-6} alkyl.

When $-NR^4R^5$ or $-NR^sR^t$ represents a heterocyclic ring, favoured heterocyclic rings are saturated or unsaturated, fused or monocyclic heterocyclic rings comprising 5, 6 or 7 ring atoms and optionally comprising 1 or 2 additional hetero-atoms, selected from O, S or N, in each ring. Favoured rings are saturated rings. Favoured rings are monocyclic rings. Favoured, additional hetero atoms are N or O. Examples of such heterocyclic rings include N- pyrrolidinyl, N-piperidinyl and N-morpholinyl.

Further examples of NR^4R^5 include NH_2 and $N(CH_3)_2$.

Suitably, R represents hydrogen or alkyl.

When R is acyl, suitable acyl groups include acetyl.

Suitably, m represents 1.

Suitably, n represents 2.

As indicated above, a compound of formula (I), and the pharmaceutically acceptable salts thereof, may exist in one of several tautomeric forms, all of which are encompassed by the present invention as individual tautomeric forms or as mixtures thereof. The compounds of formula (I) contain at least one chiral carbon, and hence they exist in one or more stereoisomeric forms. The present invention encompasses all of the stereoisomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, whether as individual stereoisomers or as mixtures of isomers, including racemates.

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a phenylene group, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein, unless otherwise stated, the term 'aryl' includes phenyl and naphthyl; any aryl group mentioned herein, unless otherwise stated, may be optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

As used herein, alkyl groups, whether present alone or as part of other groups, such as alkoxy, aralkyl or alkylcarbonyl groups, are alkyl groups having straight or branched carbon chains, containing up to 12 carbon atoms. Thus, suitable alkyl

groups are C_{1-12} alkyl groups, especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable acyl groups include alkylcarbonyl groups

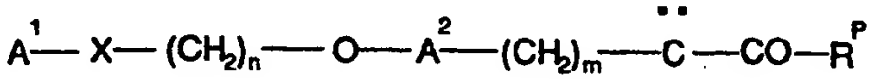
Suitable pharmaceutically acceptable salts include salts of carboxy groups and acid addition salts.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphonate, α-keto glutarate and α-glycerophosphate.

Suitable pharmaceutically acceptable solvates include hydrates.

A compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be prepared by reacting a source of a carbene of formula (II):



(II)

wherein A^1, A^2, X, m and n are as defined in relation to formula (I) and R^P is R^3 or a protecting group, with a compound of formula (III):

$$HNR^1R^2$$

(III)

wherein R^1 and R^2 are as defined in relation to the compound of formula (I); and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

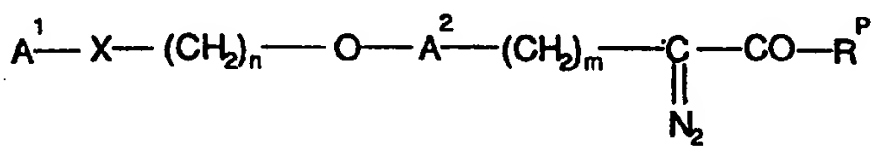
(ii) removing any protecting group; and

(iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

Suitably, R^P is R^3.

The reaction between the carbene of formula (II) and the compound of formula (III) may be carried out under conventional conditions, in any suitable solvent (conveniently the compound of formula (III) may be used as solvent) at any temperature providing a convenient rate of formation of the required product, generally at an elevated temperature, such as in the range of from 30°C to 100°C

A suitable source of a carbene of formula (II) is provided by reacting a compound of formula (IV):

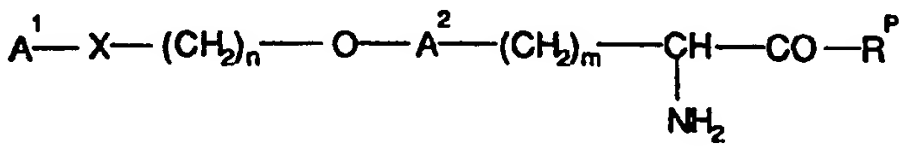


(IV)

wherein A^1, A^2, R^P, X, m and n are as defined in relation to formula (II) with a source of rhodium(II) ions, such as a rhodium (II) salt, for example rhodium (II) acetate.

The reaction conditions used for the preparation of the carbene of formula (II) from (IV) will of course depend upon the particular source of carbene chosen, but in general the above mentioned conditions for the reaction of the carbene (II) and the compound of formula (III) are appropriate.

The compound of formula (IV) may be prepared by diazotizing a compound of formula (V):



(V)

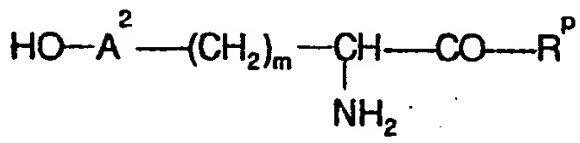
wherein A^1, A^2, R^P, X, m and n are as defined in relation to the compound of formula (IV), with an appropriate diazotizing agent, and thereafter, if required, removing any protecting group.

A suitable diazotising agent is an alkyl nitrite, such as iso-amyl nitrite.

Suitable diazotising conditions for preparing the compound of formula (IV) are conventional conditions, for example by use of an inert solvent, such as

chloroform, at any temperature providing a convenient rate of formation of the required product, generally at an elevated temperature, such as the reflux temperature of the solvent; usually the reaction is carried out in the presence of acetic acid.

A compound of formula (V) may be prepared by reacting a compound of formula (VI):



(VI)

wherein A^2, RP and m are as defined in relation to the compound of formula (V) with a compound of formula (VII):

$$A^1\text{-}X\text{-}(CH_2)_n\text{-}OL$$

(VII)

wherein A^1, X and n are as defined in relation to formula (I) and L represents a leaving group, such as a tosylate or mesylate group.

The reaction between the compound of formula (VI) and the compound of formula (VII), may be carried out in any suitable solvent, for example dimethylformamide, at a temperature which provides a suitable rate of formation of the compound of formula (V), such as at an elevated temperature, suitably in the range from 50°C to 120°C, for example at 100°C, and preferably in the presence of a base such as sodium hydride; and preferably in an inert, anhydrous atmosphere, for example dry nitrogen.

The compounds of formula (VI) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in Tetrahedron Lett., 1971, 4495, in particular the compound wherein RP is OCH_3, m is 1 and A^2 is 1,4-phenylene is a commercially available compound.

The compounds of formula (III) are known, commercially available compounds or they are compounds prepared by methods analogous to those used to prepare such compounds, for example those disclosed in J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.

The compounds of formulae (VII) are known compounds or they may be prepared according to methods used to prepare known compounds, for example those disclosed in EP 0306228.

The abovementioned conversion of a compound of formula (I) into a further compound of formula (I) includes:

a) converting one group R into another group R; and

b) converting one group $CO.R^2$ into another group $CO.R^2$.

The abovementioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

The conversion of a compound of formula (I) to a further compound of formula (I) may be carried out by using any appropriate conventional procedure.

Suitable conversions of one group R into another group R include converting a group R which represents hydrogen into a group R which represents an acyl group; such conversion may be carried out using an appropriate conventional acylation procedure, for example treating an appropriately protected compound of formula (I) with an acylating agent. Thus acetic anhydride may be used to prepare the compound of formula (I) wherein R is acetyl.

Suitable conversions of one group $CO.R^2$ into another group $CO.R^2$ include:

(i) hydrolysing one group $CO.R^{2a}$ wherein R^{2a} is alkyl, aryl or aralkyl into a group CO.OH; and

(ii) aminating one group $CO.R^{2b}$ wherein R^{2b} is alkoxy into a group $CO.NR^4R^5$ wherein R^4 and R^5 are as defined in relation to formula(I)..

Suitable hydrolysis methods for use in conversion b(i) are conventional ester hydrolysis methods, for example using an alkali hydroxide in aqueous methanol.

Suitable amination methods for conversion b(ii) include conventional methods, for example treatment with aqueous ammonia in tetrahydrofuran/methanol or treatment with an appropriate dialkylamine in a solvent such as tetrahydrofuran/methanol.

It will be appreciated that in any of the abovementioned reaction including the abovementioned conversions (a) and (b) any reactive group in the substrate molecule may be protected, according to conventional chemical practice.

In the abovementioned procedures protecting groups will be used when and as necessary in accordance with conventional procedures.

Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. Thus, for example, a suitable hydroxyl protecting group is a benzyl group.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate or sodium lauryl sulphate.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be adminstered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

The dosages regimens for the treatment of hypertension, cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt

thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

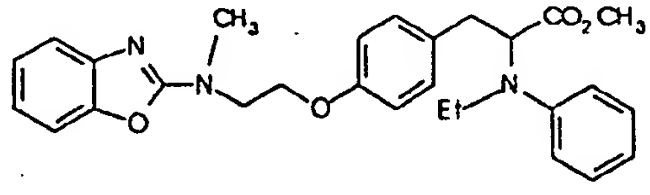
The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

No toxicological effects are indicated when a compound of the invenion is administered in the above mentioned dosage range.

The following Procedures and Examples illustrate the invention but do not limit it in any way.

Example 1

Methyl-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-((N-ethyl-N-phenyl)amino)propanoate



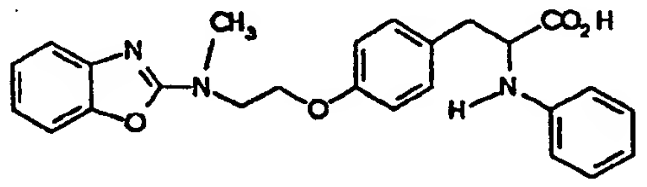
To methyl 2-amino-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-propanoate (1.1 g, 3 mmol) in chloroform (25 ml) was added acetic acid (0.5 mL, 9 mmol) then isoamyl nitrite (0.4 mL, 3 mmol). The solution was refluxed for 15 min, cooled then washed with H_2O (x 2) and $NaHCO_3$(aq). After drying ($MgSO_4$) and removal of solvent the crude diazo compound was dissolved in N-ethylaniline (25 ml) and heated to 60°C. Rh_2OAc_4 (13 mg, 0.01 eq) was added in one portion and the solution heated for 30 min. On cooling the solution was poured into 2N HCl and extracted with ethyl acetate. The organic extract was washed with 2N HCl (x 3), dried and concentrated. Chromatography (20-40% ethyl acetate/hexane) gave the title compound as a yellow oil which solidified on standing, m.p. 105-107°C (Found C, 70.97; H, 6.58; N, 8.80%. $C_{28}H_{31}N_3O_4$ requires C, 71.02; H, 6.60; N, 8.87%).

^{1}H NMR d ($CDCl_3$)

1.05 (3H,t,J=7); 3.06 (1H,dd,J=13,7); 3.27 (1H,dd,14,7); 3.34 (3H,s); 3.25-3.40 (2H,m); 3.63 (3H,s); 3.93 (2H,t,J=5); 4.22 (2H,t,J=5); 4.39 (1H,app t, J=8); 6.72 (2H,d,J=8); 6.77 (2H,d,J=9); 7.00 (1H,dt,J=8,1); 7.07 (2H,d,J=9); 7.12-7.26 (5H,m); 7.35 (1H,dd,J=8,1).

Example 2

3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(N-phenylamino)-propanoic acid



To a solution of methyl-2-amino-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]-ethoxy]phenyl]propanoate (1.84 g, 5 mmol) in chloroform was added acetic acid (0.85 mL, 15 mmol) and isoamyl nitrite (0.67 ml, 5 mmol). After heating to 60°C for 5 minutes the solution was cooled, washed with water (x 2) and $NaHCO_3$ (aq), dried and concentrated to a brown oil. The residue was dissolved in aniline (30 cm^3) and heated to 80°C prior to addition of Rh_2OAc_4 (22 mg). After 10 min the solution was cooled and chromatographed (0-10% ethyl acetate/dichloromethane to give an ester which was hydrolysed by heating a solution in methanol/water (3/1 mL) to 50°C with lithium hydroxide (2 equiv.) for 20 min. On cooling the solution was concentrated and acidified using dil. hydrochloric acid. The aqueous material was extracted with

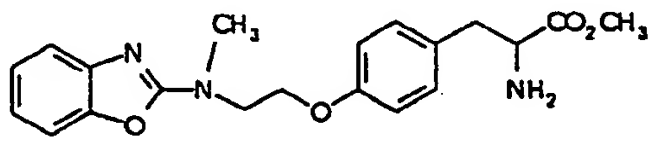
dichloromethane (x3) and the combined extracts dried and concentrated. The residue was chromatographed (2% methanol in dichloromethane) to give the product as a white solid, mp 147-150°C (Found C, 69.47; H, 5.90; N, 9.84% $C_{25}H_{25}N_3O_4$ requires C, 69.59; H, 5.84; N, 9.74%).

^{1}H NMR d (DMSO)

2.84-3.02 (2H,m); 3.21 (3H,s); 3.86 (2H,t,J=5.5); 4.03 (1H,m); 4.21 (2H,t,J=5.5); 5.8 (1H,br); 6.49-6.57 (2H,m); 6.84 (2H,d,J=9); 6.95-7.23 (6H,m); 7.25 (1H,d,J=7.5); 7.36 (1H,d,J=8); 12.55 (1H,br).

Procedure 1

Methyl 2-amino-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-propanoate



Sodium hydride (60% dispersion in oil; 1.00 g) was added portionwise to a stirred solution of tyrosine methyl ester (3.90 g) in dry N,N-dimethylformamide (70 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 minutes prior to the addition of a solution of 2-[N-(2-benzoxazolyl)-N-methylamino]-ethanol methanesulphonyl ester *(Eur. Patent Appl., Publication No.* 0306228) (5.90 g) in dry N,N-dimethylformamide (30 mL). The mixture was heated at 100°C for 6 hrs, cooled, diluted with iced water (500 mL) and extracted with ethyl acetate (3x250 mL). The combined ethyl acetate layers were washed with brine (2x1L), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with 5% methanol in dichloromethane as eluent to afford an oil. This was crystallised from ethyl acetate to afford the title compound, mp 95-6°C.

^{1}H NMR d ($CDCl_3$)

1.45 (2H,br,exchanges with D_2O); 2.81 (1H,dd); 3.01 (1H,dd); 3.33 (3H,s); 3.67 (1H,dd); 3.70 (3H,s); 3.95 (2H,t); 4.25 (2H,t); 6.83 (2H,d); and 6.95-7.40 (6H,complex).

DEMONSTRATION OF EFFICACY OF COMPOUNDS

Obese Mice, Oral Glucose Tolerance Test.

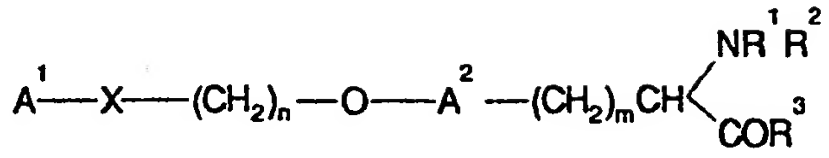
C57bl1/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3 g/kg). Blood samples for glucose analysis were taken 0, 45, 90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control groups. 8 mice were used for each treatment.

Activity table

Example No.	Level in diet (mmol.kg^{-1} of diet)	% Reduction in area under blood glucose curve
1	300	50
2	1000	55
	30	31

CLAIMS/A

1. A compound of formula (I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

A^2 represents a benzene ring having three optional substituents;

R^1 represents a hydrogen atom or an alkyl group;

R^2 represents an aryl group;

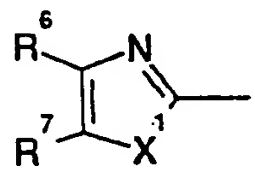
R^3 represents OT^1 wherein T^1 represents hydrogen, alkyl, aryl or aralkyl, or R^3 represents-NR^4R^5 wherein R^4 and R^5 each independently represent hydrogen or alkyl or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring;

X represents O, S or NR wherein R represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

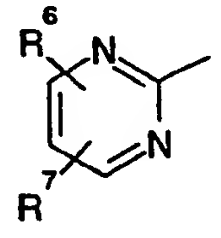
m represents an integer in the range of from 1 to 6; and

n represents an integer in the range of from 2 to 6.

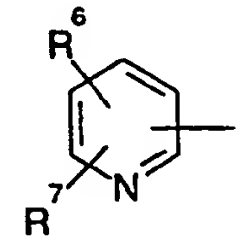
2. A compound according to claim 1, wherein A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

wherein:

R^6 and R^7 each independently represents a hydrogen or halogen atom, an alkyl or alkoxy group or a substituted or unsubstituted aryl group or when R^6 and R^7 are each attached to adjacent carbon atoms, then R^6 and R^7 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^6 and R^7 together is substituted or unsubstituted; and in the moiety of formula (a) X^1 represents oxygen or sulphur.

3. A compound according to claim 1 or claim 2, wherein R^1 represents hydrogen or a C_{1-6} alkyl group.

4. A compound according to any one of claims 1 to 3, wherein R^1 represents hydrogen or methyl.

5. A compound according to any one of claims 1 to 4, wherein R^2 represents phenyl.

6. A compound according to claim 5, wherein R^3 represents OT^1 wherein T^1 is C_{1-6} alkyl.

7. A compound according to any one of claims 1 to 4, wherein R^3 represents - NR^4R^5.

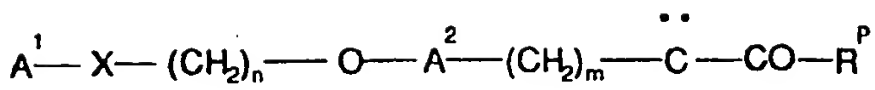
8. A compound according to claim 7, wherein R^4 and R^5 each independently represent hydrogen or C_{1-6} alkyl.

9. A compound according to any one of claims 1 to 8, wherein m is 1 and n is 2.

10. A compound according to claim 1 being:

methyl-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-((N-ethyl-N-phenyl)amino)propanoate; or
3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(N-phenylamino)-propanoic acid; or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof.

11. A process for the preparation of a compound of formula (I) according to claim 1, or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises:
by reacting a source of a carbene of formula (II):



(II)

wherein A^1, A^2, X, m and n are as defined in relation to formula (I) and R^P is R^3 or a protecting group, with a compound of formula (III):

$$HNR^1R^2$$

(III)

wherein R^1 and R^2 are as defined in relation to the compound of formula (I); and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any protecting group; and

(ii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

12. A pharmaceutical composition comprising a compound of formula (I) according to claim 1, or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

13. A compound of formula (I) according to claim 1, or tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

14. A compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

15. A method for the treatment and/or prophylaxis of hyperglycaemia hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a

pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

16. The use of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/01449

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D263/58 C07D213/74 C07D239/42 A61K31/42 A61K31/44 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 19702 (PFIZER INC) 26 December 1991 cited in the application see claims	1,2, 12-16
A	EP,A,0 306 228 (BEECHAM GROUP PLC) 8 March 1989 see claims	1,2, 12-16
A	WO,A,92 02520 (BEECHAM GROUP PLC) 20 February 1992 see claims	1,2, 12-16
P,X	WO,A,94 01420 (SMITHKLINE BEECHAM PLC) 20 January 1994 cited in the application see page 65; claims	1,2, 12-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 1994	29. 07. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/01449

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The definition of radical A1 as aromatic heterocyclic group is too broadly formulated to permit an adequate search. The search has essentially been limited to the compounds of formula I supported by the examples.
Claims searched incompletely: 1-9, 11-16

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/EP 94/01449

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9119702	26-12-91	US-A-	5089514	18-02-92
		AU-B-	646052	03-02-94
		AU-A-	7995691	07-01-92
		EP-A-	0533781	31-03-93
		US-A-	5306726	26-04-94
EP-A-0306228	08-03-89	AU-A-	2173888	09-03-89
		CA-A-	1328452	12-04-94
		JP-A-	1131169	24-05-89
		US-A-	5002953	26-03-91
		US-A-	5232925	03-08-93
		US-A-	5194443	16-03-93
		US-A-	5260445	09-11-93
WO-A-9202520	20-02-92	AU-B-	646491	24-02-94
		AU-A-	8317891	02-03-92
		CA-A-	2093146	07-02-92
		EP-A-	0542816	26-05-93
		JP-T-	6500538	20-01-94
		NZ-A-	239265	25-02-94
WO-A-9401420	20-01-94	AU-B-	4506893	31-01-94